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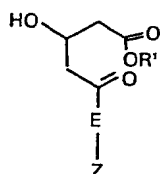
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Oxo-analogs of mevinolin-like antihypercholesterolemic agents.

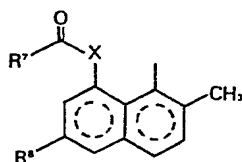
Mevinolin-like compounds of the structural formula:



are disclosed wherein:

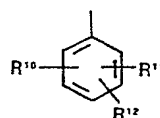
R' is, e.g., hydrogen or C1-4alkyl;
 E is $-\text{CH}_2\text{CH}_2-$, $-\text{CH}=\text{CH}-$, or $-(\text{CH}_2)_n-$; and
 Z is

1)



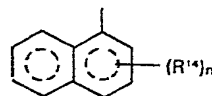
wherein X is $-\text{O}-$ or $-\text{NR}^*$ wherein R* is hydrogen or C1-3alkyl;
 R' is C2-8alkyl; and
 R'' is hydrogen or $-\text{CH}_3$;

2)



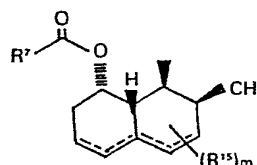
wherein R¹⁰, R¹¹ and R¹² are independently, e.g., hydrogen, halogen or C1-4alkyl;

3)



wherein n is 0-2 and R¹⁴ is halo or C1-4alkyl; or

4)



/...

wherein the dotted lines represent possible double bonds
there being 0, 1 or 2 double bonds;

m represents 1, 2 or 3; and

Rⁿ is methyl, hydroxy, C1-alkoxy, oxo, or halo.

Those compounds are potent HMG-CoA reductase
inhibitors possessing one less asymmetric center.

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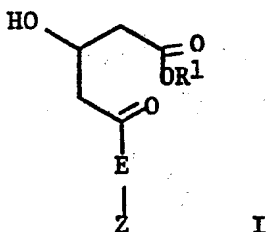
TITLE OF THE INVENTION

OXO-ANALOGS OF MEVINOLIN-LIKE ANTIHYPER-
CHOLESTEROLEMIC AGENTS

5 SUMMARY OF THE INVENTION

This invention is concerned with novel
compounds of structural formula I:

10



15 wherein Z is a variety of mono- and bi-carbocyclic
moieties with various substituents well known to
those skilled in the art of 3-hydroxy-3-methyl-
glutaryl Coenzyme A (HMG-CoA) reductase inhibitors
useful in the treatment of familial hyper-
20 cholesterolemia, hyperlipemia and atherosclerosis.

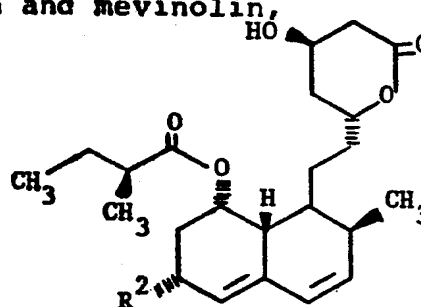
The invention is also concerned with novel processes for the preparation of the novel compounds; pharmaceutical formulations comprising a novel compound as active ingredient; and a method of
5 treating familial hypercholesterolemia, hyperlipemia, and atherosclerosis.

BACKGROUND OF THE INVENTION

Over the past several years a number of
10 structurally related antihypercholesterolemic agents acting by inhibition of HMG-CoA reductase have been reported in the patent literature and elsewhere. The compounds have varied from the natural fermentation
15 products, compactin and mevinolin,

15

20

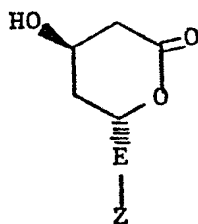


Compactin ($R^2=H$)
Mevinolin ($R^2=CH_3$)

25 to di- and tetrahydro derivatives thereof; to analogs with different esters in the 8-position of the polyhydronaphthalene moiety, to totally synthetic analogs, wherein the polyhydronaphthalene moiety is replaced by substituted mono- and bicyclic aromatics,
30 and biphenyls. But in all instances the active compound included a 4-hydroxytetrahydropyran-2-one ring or the corresponding 3,5-dihydroxy acid, or derivatives thereof, formed by opening the pyranone ring such as:

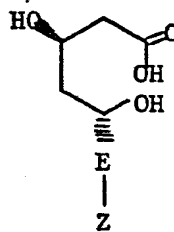
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II

or



IIa

4-hydroxytetrahydropyran-2-one

3,5-dihydroxy-acid

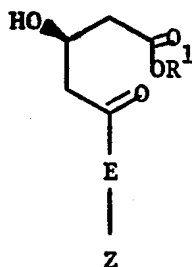
- 10 In all of these compounds the 3,5-dihydroxy acid or corresponding lactone moiety is present and the particular stereochemistry depicted is essential for manifestation of the optimum enzyme inhibitory activity.
- 15 Now with the present invention there are provided compounds structurally related to those lactones and dihydroxy acids that do not have the 5-hydroxy functionality, do not form a lactone ring, and are incapable of stereochemical variation at the
- 20 5-position of the acid because the 5-carbon is not asymmetric. On the contrary, the 5-carbon carries an oxo function which greatly facilitates the total synthesis of active compounds in that by eliminating one asymmetric center it is unnecessary to separate
- 25 diastereoisomers or to conduct a stereoselective synthesis to obtain optimum enzyme inhibitory activity. It is believed that structures I are reduced in situ to generate the "active" inhibitors of structure II or IIa.
- 30 The active compounds of this invention are useful in either the racemic form or as the 3(R)-isomer. Those compounds produced by total synthesis are obtained initially as racemates, but

may be resolved by standard methods into 3(R)- and 3(S)-isomers. Compounds of Structure I which are synthesized starting from natural fermentation products such as mevinolin and its analogs are
 5 obtained as the optically pure 3(R)-isomers.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of this invention have structural formula:

10



15

wherein

R¹ is

20

- 1) hydrogen,
- 2) C₁₋₄alkyl,
- 3) 2,3-dihydroxypropyl,
- 4) alkali metal cation, such as Na⁺, or K⁺, or

25

- 5) ammonium of formula $\text{NR}^3\text{R}^4\text{R}^5\text{R}^6$ ⁺ wherein R³, R⁴, R⁵ and R⁶ are independently hydrogen or C₁₋₄alkyl or two of R³, R⁴, R⁵ and R⁶ are joined together to form a 5 or 6-membered heterocycle such as pyrrolidino or piperidino with the nitrogen to which they are attached;

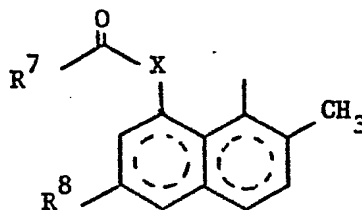
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E is - CH₂CH₂-, -CH=CH-, or (CH₂)₃-; and

Z is 1)

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5

wherein the dotted lines represent all of the possible oxidation states of the bicyclic system such as naphthalene, dihydro-, tetrahydro-, hexahydro-, octahydro-, and decahydronaphthalene;

10

X is -O- or >NR^9 wherein

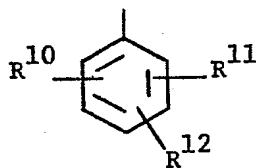
R^9 is H or C_{1-3} alkyl;

R^7 is C_{2-8} alkyl; and

15

R^8 is H or $-\text{CH}_3$;

2)



20

wherein R^{10} , R^{11} and R^{12} are independently

25

- a) hydrogen,
- b) halogen, such as bromo, chloro or fluoro,
- c) C_{1-4} alkyl,
- d) halo- C_{1-4} alkyl,
- e) phenyl either unsubstituted or substituted with one or more of

30

- i) C_{1-4} alkoxy,
- ii) C_{1-4} alkyl,
- iii) C_{2-8} alkanoyloxy, or
- iv) halo- C_{1-4} alkyl,

v) halo, such as bromo, chloro or fluoro,

f) OR^{13} wherein R^{13} is

i) hydrogen,

ii) C_{1-8} alkanoyl,

iii) benzoyl,

iv) phenyl,

v) halophenyl,

vi) phenyl- C_{1-3} alkyl, either unsubstituted or substituted with one or more of halogen,

C_{1-4} alkoxy, C_{1-4} alkyl or halo- C_{1-4} alkyl,

vii) C_{1-9} alkyl,

viii) cinnamyl,

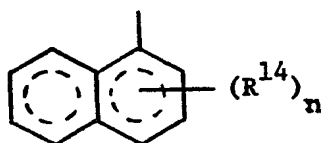
ix) halo- C_{1-4} alkyl,

x) allyl,

xi) C_{3-6} cycloalkyl- C_{1-3} alkyl,

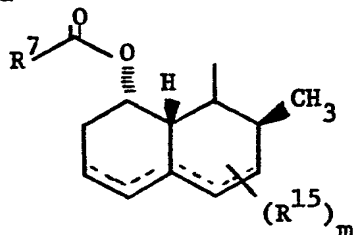
xii) adamantyl- C_{1-3} alkyl,

3)



wherein n is 0-2, and R^{14} is halo such as chloro, bromo or fluoro, or C_{1-4} alkyl, and

4)



wherein the dotted lines represent possible double bonds there being 0, 1 or 2 double bonds;

m represents 1, 2 or 3; and

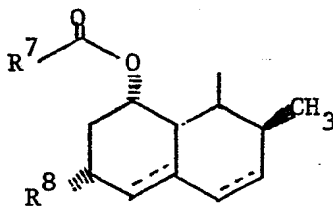
R^{15} is 1) methyl,
2) hydroxy,
3) C_{1-4} alkoxy,
4) oxo or
5) halo.

Preferred embodiments of the novel compounds are those in which:

R^1 is hydrogen, an alkali metal cation or an ammonium cation;

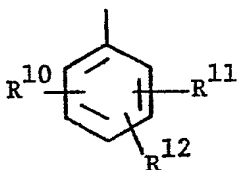
E is $-CH=CH-$ or $-CH_2CH_2-$; and

Z is 1)



wherein $R^7-\overset{\overset{O}{\parallel}}{C}-$ is 2-methylbutyryl or 2,2-dimethylbutyryl;

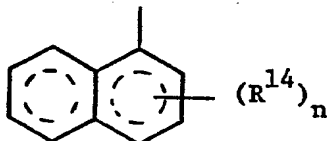
2)



wherein R^{10} , R^{11} and R^{12} are independently
a) halogen,

- b) C_{1-4} alkyl,
c) halo- C_{1-4} alkyl,
d) phenyl with 1 to 3 substituents selected
from halo, C_{1-4} alkyl or C_{1-4} alkoxy,
5 e) OR^{13} , wherein R^{13} is
i) phenyl,
ii) halophenyl,
iii) phenyl substituted with 1-3
substituents selected from
10 halogen, and C_{1-4} alkyl,
iv) phenyl- C_{1-3} alkyl, either
unsubstituted or substituted with
one or more of halogen, C_{1-4}
alkoxy, C_{1-4} alkyl or
15 halo- C_{1-4} alkyl; or

3)

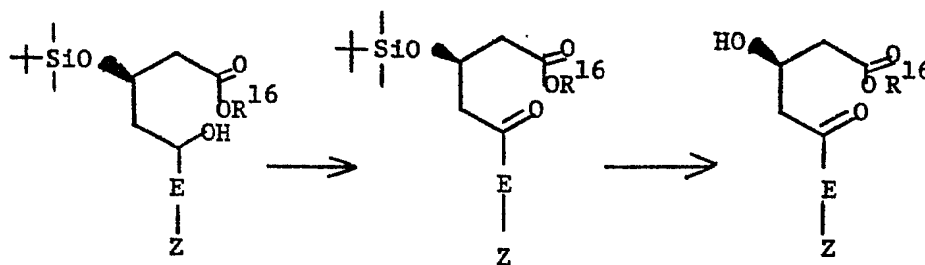


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wherein n is 0, 1 or 2 and R^{14} is methyl
25 and the ring system is naphthalene or 5,6,7,8-
tetrahydronaphthalene.

One novel process for preparing the novel
compounds of this invention is particularly useful
30 when starting with compounds with a pre-formed
4-hydroxytetrahydropyran-2-one moiety or the
corresponding 3,5-dihydroxy acid and is illustrated
as follows:

5

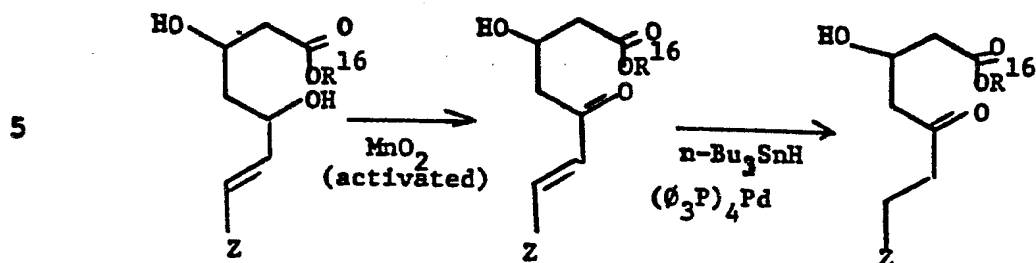


- 10 wherein R^{16} is C_{1-4} alkyl, especially methyl. After protecting the 4-hydroxyl of the lactone with a dimethyl-tert-butylsilyl group and preparing an alkyl ester by known procedures, the resulting 5-hydroxy of the open-chain acid is oxidized to the ketone.
- 15 Suitable oxidizing agents include: pyridinium chlorochromate in a chlorinated alkane such as methylene chloride or chloroform at about 0° to about 25°C for about 1 to 4 hour; oxalyl chloride in dimethylsulfoxide at about -70° to about -40°C for
- 20 about 0.25 to 0.5 hours; trifluoroacetic anhydride in dimethylsulfoxide at about -70° to -40°C for about 0.25 to 0.5 hour; and pyridinium dichromate in dimethyl formamide at 0° to 25°C for 1 to 8 hours.

25 The silyl ether group is then hydrolyzed by treatment with acetic acid and tetrabutylammonium fluoride in tetrahydrofuran.

A related procedure is available for preparing compounds of this invention wherein E represents $-\text{CH}_2-\text{CH}_2-$. It obviates the need for

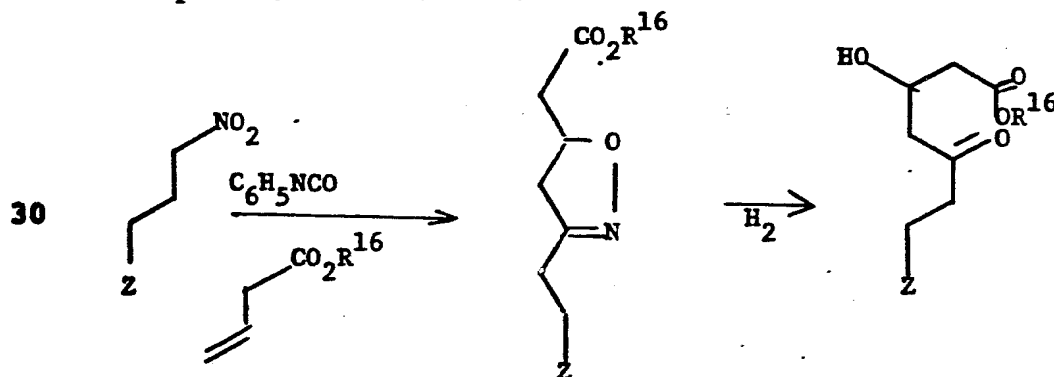
30 protection of the 3-hydroxy group before oxidizing the 5-hydroxy and is represented as follows:



10

In the first step the dihydroxy compound is treated with activated manganese dioxide in a chlorinated hydrocarbon such as chloroform, methylene chloride, 1,2-dichloroethane or the like at about 0°C to 40°C preferably at ambient temperature for about 15 to 30 hours. The 5-oxo compound produced is then treated with tri-*n*-butyltin hydride and tetrakis(triphenylphosphine)palladium(0) in an ethereal solvent such as ether, THF, 1,2-dimethoxyethane or the like, at about ambient temperature for about 15 to 30 hours.

Alternatively, if the 3-hydroxy-5-oxo-carboxylic acid moiety is being synthesized, the 5-oxo group is realized directly by a process which is another embodiment of this invention and which is exemplified as follows:



The nitro compound is treated with a C_{1-4} alkyl 3-butenate, preferably methyl 3-butenate, and an aromatic isocyanate such as p-toluoyl isocyanate, p-chlorophenyl isocyanate, phenyl isocyanate or the like, preferably the latter, and a bit of triethylamine as a catalyst in an inert organic solvent such as toluene, benzene, xylene, or the like at about 15 to 30°C, preferably about room temperature for about 5 to about 24 hours.

The resulting isoxazoline is reduced catalytically with palladium on carbon, platinum oxide or the like in an inert organic solvent such as a C_{1-3} alkanol, acetic acid or the like containing a little water in the presence of boric acid at about 15 to 30°C and about 1-2 atmospheres of hydrogen pressure for about 1 to 6 hours.

The ester resulting from either of the foregoing synthetic schemes is readily saponified to the corresponding carboxylic acid salt by treatment with aqueous alkali such as potassium or sodium hydroxide to form the potassium or sodium salt respectively or with a quaternary ammonium hydroxide of formula $HONR^3R^4R^5R^6$ wherein none of the R groups is hydrogen to form the quaternary ammonium salt.

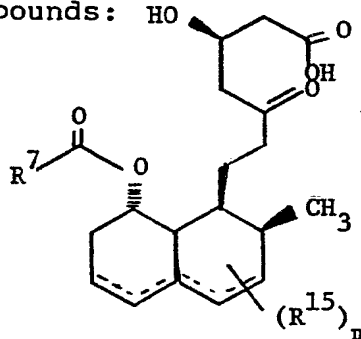
Acidifying any of these salts with a mineral acid results in the formation of the free carboxylic acid.

The acids are readily converted back to salts by treatment with the appropriate base or to esters by treatment with a C_{1-4} alkanol in the presence of a catalytic amount of an acid such as hydrogen chloride at about 50 to 100°C for about 3 to 6 hours.

The previously described salts are converted back to esters by treatment with an alkyl halide such as 2,3-dihydroxypropyl iodide in an aprotic solvent such as N,N-dimethylformamide, N-methylpyrrolidone or hexamethylphosphoramide at about 25 to 100°C for about 18 to 36 hours.

Those compounds, wherein Z is of the sub-type (4), i.e., in which the polyhydronaphthalene moiety is substituted with hydroxy or oxo, halo or alkoxy are prepared from the corresponding substrate in which the 5-oxo group of the heptenoic acid is already in place. The processes, as applied to the 5-hydroxy analogs or the corresponding lactones, are disclosed in EP application 76601, British patents 2,111,052 and 2,075,013, EP application 74222, and Japanese published applications J58010572 and J57155995. Using those processes there are produced the following compounds:

20



25

Double Bonds	R ⁷	(R ¹⁵) _m
3,4:4a,5	1-methylpropyl	6-OH
3,4:4a,5	1,1-dimethylpropyl	6-OH
4,4a	1-methylpropyl	3-OH, 5-OH
4,4a	1,1-dimethylpropyl	3-OH, 5-OH
4,4a:5,6	1-methylpropyl	3-OH
4,4a:5,6	1,1-dimethylpropyl	3-OH
-	1-methylpropyl	6-OH

30

	-	1,1-dimethylpropyl	6-OH
	-	1-methylpropyl	3-OH
	-	1,1-dimethylpropyl	3-OH
	4,4a	1-methylpropyl	6-OH
5	4,4a	1,1-dimethylpropyl	6-OH
	4,4a	1-methylpropyl	3-OH
	4,4a	1,1-dimethylpropyl	3-OH
	4a,5	1-methylpropyl	6-OH
	4a,5	1,1-dimethylpropyl	6-OH
10	4a,5	1-methylpropyl	3-OH
	4a,5	1,1-dimethylpropyl	3-OH
	4,4a	1-methylpropyl	3-OH, 5=O
	4,4a	1,1-dimethylpropyl	3-OH, 5=O
	4,4a	1-methylpropyl	3=O, 5=O
15	4,4a	1,1-dimethylpropyl	3=O, 5=O
	-	1-methylpropyl	3-OH, 5-OH
	-	1,1-dimethylpropyl	3-OH, 5-OH
	4,4a	1-methylpropyl	3-Cl, 5-Cl
	4,4a	1,1-dimethylpropyl	3-Cl, 5-Cl
20	4,4a	1-methylpropyl	3-OCH ₃ , 5-OH
	4,4a	1,1-dimethylpropyl	3-OCH ₃ , 5-OH
	4,4a	1-methylpropyl	3-OC ₂ H ₅ , 5-OH
	4,4a	1,1-dimethylpropyl	3-OC ₂ H ₅ , 5-OH
	4,4a	1-methylpropyl	3-OC ₄ H ₉ , 5-OH
25	4,4a	1,1-dimethylpropyl	3-OC ₄ H ₉ , 5-OH
	4,4a	1-methylpropyl	6-CH ₃ , 3-OH, 5-OH
	4,4a	1,1-dimethylpropyl	6-CH ₃ , 3-OH, 5-OH

The novel pharmaceutical composition of this
 invention comprises at least one of the compounds of
 formula I in association with a pharmaceutical
 vehicle or diluent. The pharmaceutical composition
 can be formulated in a classical manner utilizing

solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration. The compounds can be administered by an oral route, for example, in the form of tablets, capsules, granules or powders, or they can be administered by a parenteral route in the form of injectable preparations.

A typical capsule for oral administration contains active ingredient (25 mg), lactose (75 mg) and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

A typical injectable preparation is produced by aseptically placing 25 mg of a water soluble salt of sterile active ingredient into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 ml of physiological saline, to produce an injectable preparation.

The novel method of treating atherosclerosis, familial hypercholesterolemia, or hyperlipemia of this invention comprises administration of an effective antihypercholesterolemic amount of a compound of Formula I to a patient in need of such treatment.

The dose to be administered depends on the unitary dose, the symptoms, and the age and the body weight of the patient. A dose for adults is preferably between 20 and 2,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1-4 times per day.

The compounds of this invention also have useful antifungal activities. For example, they may be used to control strains of Penicillium sp.,

Aspergillus niger, Cladosporium sp., Cochliobolus
miyabeorus and Helminthosporium cynodnotis. For
those utilities they are admixed with suitable
formulating agents, powders, emulsifying agents or
5 solvents such as aqueous ethanol and sprayed or
dusted on the plants to be protected.

This invention can be illustrated by the
following examples.

10

EXAMPLE 1

7-[2(S),6(R)-Dimethyl-8(S)-(2(S)-methylbutyryloxy)-
1,2,6,7,8,8a(R)-hexahydro-1(S)-naphthyl]-3(R)-hydroxy-
5-oxoheptanoic acid

15

Step A: Preparation of 6(R)-[2-(8(S)-(2(S)-methyl-
butyryloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,
8a(R)-hexahydronaphthyl-1(S))-ethyl]-4(R)-
(dimethyl-tert-butylsilyloxy)-3,4,5,6-tetra-
hydro-2H-pyran-2-one

20

Mevinolin (4.04 g, 0.01 mol) was dissolved
in 25 ml of dry dimethylformamide (DMF) and treated
with 2.7 g (0.04 mol) of imidazole and 3 g (0.02 mol)
of dimethyl-tert-butylsilyl chloride, and the
solution was stirred under nitrogen overnight. The
mixture was poured into 200 ml of ether, washed with
25 2 X 50 ml of water, 1 X 25 ml of 1N hydrochloric
acid, 1 X 25 ml of saturated aqueous sodium carbonate
and 2 X 50 ml of brine, dried over $MgSO_4$ and
concentrated to dryness. The residue was chromato-
graphed on a "Still" column of silica gel (6.0 X 17.7
30 cm, 230-400 mesh) by elution with 45% ether in hexane
(V/V) collecting 20 ml fractions. The fractions
containing the product (21-52) were combined and
concentrated to dryness to give 5.2 of oil.

Step B: Preparation of Methyl 7-[2(S), 6(R)-Dimethyl-8(S)-(2(S)-methylbutyryloxy)-1,2,6,7,8,8a(R)-hexahydro-1(S)-naphthyl]-3(R)-(tert-butyl dimethylsilyloxy)-5(R)-hydroxyheptanoate

5 The silyl ether from Step A (1.03 g, 0.002 mol) was dissolved in 10 ml of methanol, treated with 2 ml of 1N aqueous sodium hydroxide and the mixture was stirred for 2 hours at room temperature. The methanol was evaporated under reduced pressure and
10 the residue was freed of water by azeotropic distillation of 4 X 10 ml of toluene. The solid residue was dissolved in 5 ml of dry DMF, treated with 300 μ l, (0.68 g, 0.0048 mol) of methyl iodide and the mixture was stirred overnight at room
15 temperature. The mixture was poured into 100 ml of ether and washed with 20 ml of water and 20 ml of brine, dried (MgSO_4) and concentrated to dryness to give 1.0 g of residue (contained DMF). This material was chromatographed on a "Still" column of silica gel
20 (6.0 X 17.7 cm, 230-400 mesh) by elution with 45% ether in hexane (V/V) collecting 20 ml fractions. Fractions 32-50 containing the major component were combined and concentrated to dryness to give 576 mg of oily product.

25

Step C: Preparation of Methyl 7-[2(S), 6(R)-Dimethyl-8(S)-(2(S)-methylbutyryloxy)-1,2,6,7,8,8a(R)-hexahydro-1(S)-naphthyl]-3(R)-(tert-butyl dimethylsilyloxy)-5-oxoheptanoate

30

The ester from Step B (586 mg, 0.001 mol) was dissolved in 10 ml of methylene chloride and cooled to 0°C. Pyridine chlorochromate (0.56 g, 0.0026 mol) was added and the stirred mixture was

allowed to warm spontaneously over 2 hours.
Additional pyridine chlorochromate (224 mg, 0.001
mol) was added and stirring was continued another
hour. The methylene chloride was evaporated in
5 vacuo. The residue was suspended in 5 ml. ether,
placed on top of a 4 X 40 cm column of silica gel
(70-230 mesh) and eluted with 40% ether in hexane
(V/V) collecting 15 ml fractions. Fractions 10-23
were combined and concentrated to 130 mg. of oily
10 product.

Step D: Preparation of Methyl 7-[2(S), 6(R)-Dimethyl-
8(S)-(2(S)-methylbutyryloxy)-1,2,6,7,8,8a(R)-
hexahydro-1(S)-naphthyl]-3(R)-hydroxy-5-oxo-
15 heptanoate

The silyl ether from Step C (230 mg, 0.00024
mol) was dissolved in 5 ml of tetrahydrofuran (THF)
and treated with 54 μ l, (0.057 g, 0.00095 mol) of
acetic acid and 710 μ l (1M in THF, 0.00071 mol) of
20 $\text{Bu}_4\text{N}^+\text{F}^-$
tetrabutylammonium fluoride ($\text{Bu}_4\text{N}^+\text{F}^-$) and the
mixture was stirred overnight at room temperature.

Another 57 μ l of acetic acid and 710 μ l of $\text{Bu}_4\text{N}^+\text{F}^-$
25 were added and stirring was continued an additional
24 hours. The mixture was poured into 100 ml of
ether and washed with 1 x 5 ml of 1N hydrochloric
acid, 1 x 10 ml of saturated aqueous sodium
bicarbonate and 2 x 10 ml of brine and dried
30 (MgSO_4). Concentration to dryness gave 120 mg of
an oil. The oil was chromatographed on a "Still"
column of silica gel (1.5 x 17.7 cm, 230-400 mesh) by
elution with 5% acetone in methylene chloride (v/v)

collecting 5 ml fractions. Fractions 12-20 containing the product were combined and concentrated to dryness to give 53 mg of solid (m.p. 64-66°C).

Recrystallization of a sample from hexane gave

5 material with m.p. 67-68°C.

Analysis for $C_{25}H_{38}O_6$ (434.55): Calc: C, 69.09; H, 8.81.

Found: C, 69.30; H, 9.38.

10 Step E: Preparation of 7-[2(S),6(R)-Dimethyl-8(S)-(2(S)-methylbutyryloxy)-1,2,6,7,8,8a(R)-hexahydro-1(S)-naphthyl]-3(R)-hydroxy-5-oxoheptanoic acid

The ester from Step D (43 mg, 0.0001 mol) was dissolved in 5 ml of methanol and treated with 2 ml of 0.1N sodium hydroxide (0.0002 mol) and stirred overnight at room temperature. The methanol was evaporated in vacuo and the residue was acidified with 1N hydrochloric acid and extracted with ether. The ether extract was washed with 3 x 10 ml of brine and dried over $MgSO_4$. Concentration to dryness provided 36 mg of solid which after recrystallization from ether/hexane had m.p. 102-103°C.

20 Analysis for $C_{24}H_{36}O_6$ (420.53): Calc: C, 68.54; H, 8.63.

25 Found: C, 68.57; H, 8.88.

Employing the procedure substantially as described in Example 1, Steps A through E, but substituting for the mevinolin used in Step A, equimolar amounts of the lactones described in Table I there are produced the corresponding 5-oxo-carboxylic acids, salts, and esters also described in Table I in accordance with the following reaction scheme:

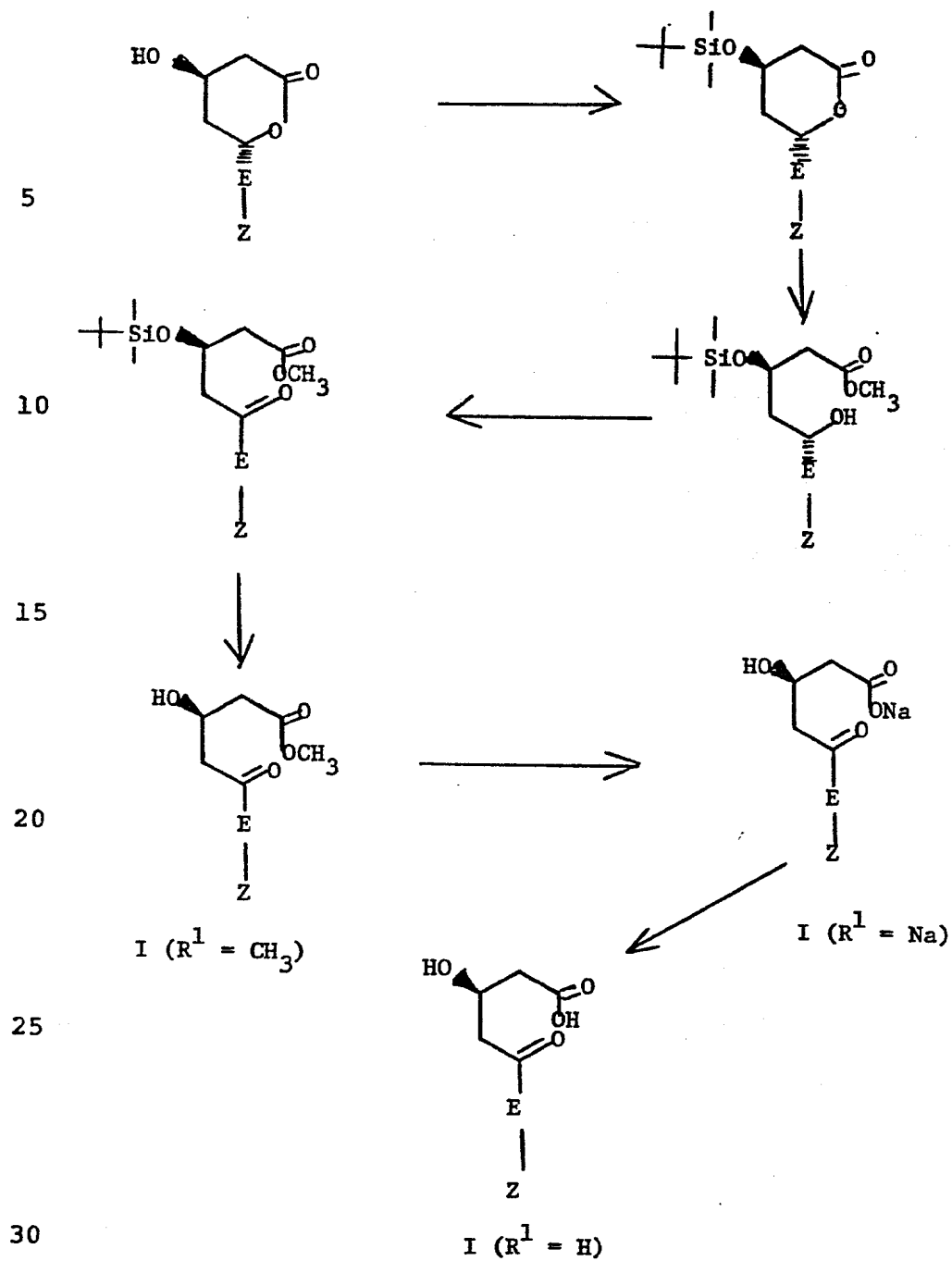


TABLE I

1)

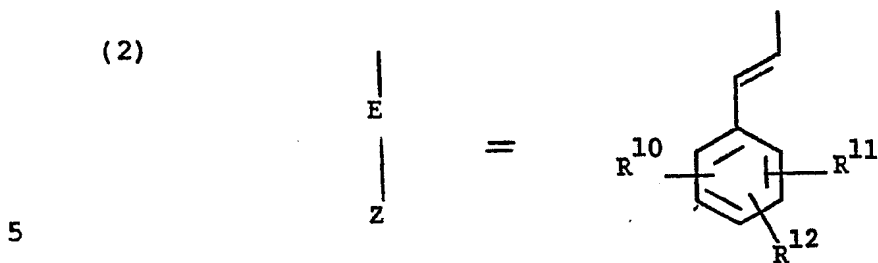
5

$\begin{array}{c} | \\ E \\ | \\ Z \end{array} =$

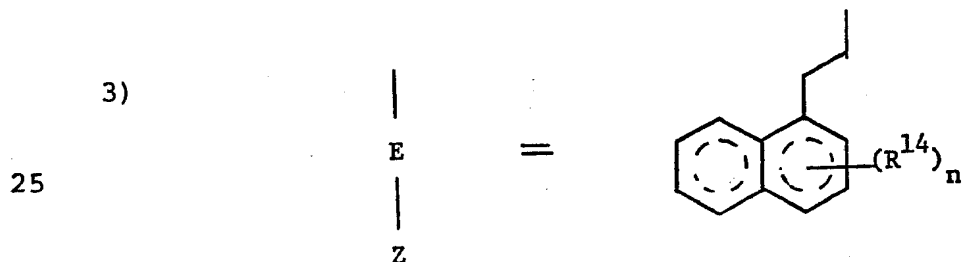
	R^7 C=O	R^8	X	a	b
10	2(S)-methylbutyryl	-CH ₃	O	single	double
	2(S)-methylbutyryl	-CH ₃	O	single	single
	2(R)-methylbutyryl	-CH ₃	O	double	double
	2,2-dimethylbutyryl	-CH ₃	O	double	double
15	2,2-dimethylbutyryl	-CH ₃	O	single	double
	2,2-dimethylbutyryl	-CH ₃	O	single	single
	acetyl	-CH ₃	O	double	double
	2(S)-methylbutyryl	H	O	single	single
	2,2-dimethylbutyryl	H	O	double	double
20	2,2-dimethylbutyryl	H	O	single	single
	2,2-dimethylbutyryl	-CH ₃	NH	single	single
	2-methyl-2-ethylbutyryl	-CH ₃	NH	single	single
	2-methylbutyryl	-CH ₃	NH	single	single
	4-fluorobenzoyl	-CH ₃	NH	single	single
25	4-fluorophenylacetyl	-CH ₃	NH	single	single
	4- <u>tert</u> -butylbenzoyl	-CH ₃	NH	single	single
	acetyl	-CH ₃	NH	double	double
	acetyl	-CH ₃	NCH ₃	single	single
	2,2-dimethylbutyryl	-CH ₃	NCH ₃	single	single
30	2,2-dimethylbutyryl	-CH ₃	NH	double	double

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	R^{10}	R^{11}	R^{12}
	6-(4-fluoro-3-methylphenyl)-	2-methyl	4-methyl
10	6-(4-fluorophenyl)-	2-chloro	4-chloro
	6-(4-chlorophenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)-	2-chloro	4-chloro
	6-(4-fluoro-3-methylphenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)-	2-methyl	4-methyl
15	6-(3,5-dimethylphenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)-	2-methyl	5-methyl
	6-(4-fluorophenyl)-	2-methyl	4-methyl
	6-(4-fluoro-3-methylphenyl)-	2-methyl	4-chloro
	6-(4-fluorobenzyloxy)	2-chloro	4-chloro
20	6-(4-fluoro-3-methylphenyl)	2-chloro	4-methyl



	n	R^{14}	
30	1	2-methyl	naphthyl
	0	-	naphthyl
	2	2,6-dimethyl	naphthyl
	1	2-methyl	5,6,7,8-tetrahydronaphthyl

EXAMPLE 2

7-(4'-Fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl)-3-hydroxy-5-oxoheptanoic acid

5 Step A: Preparation of Methyl 3-(4'-Fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl)propionate

A solution of 1.716 g (13 mmol) of dimethyl malonate in 5 ml of DMF was added dropwise to a stirred suspension of sodium hydride (50% oil dispersion, 0.624 g, 13 mmol) in 15 ml of DMF and
10 stirring was continued under nitrogen for 0.5 hour. The mixture was treated with ice bath cooling, with a solution of 3.1 g (11.8 mmol) of 2-chloromethyl-4'-fluoro-3,3',5-trimethyl-1,1'-biphenyl in 10 ml of DMF. The resulting mixture was stirred at 0°C for 10
15 minutes, at room temperature for 0.5 hour, and heated on a steam bath for 1 hour. Sodium chloride (0.759 g, 13 mmol) and 0.234 ml (13 mmol) of water were added to the reaction mixture and it was heated at reflux for 16 hours. The reaction mixture was cooled,
20 poured into cold water and extracted with ether twice. The combined extracts were washed with dilute hydrochloric acid, dried over MgSO_4 , filtered and concentrated to dryness in vacuo to give 3.42 (11.38 mmol, 96%) of the desired product as a brown oil
25 which was used directly in the next step without purification.

30 nmr (CDCl_3) δ : 2.27 (6H, a methyl singlet and a methyl doublet), 2.3 (2H, m), 2.34 (3H, s), 2.9 (2H, m), 3.60 (3H, s), 6.84 (H, bs), 7.1-7.2 (4H, m).

Step B: Preparation of 3-(4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl)propanol

A solution of 3.42 g (11.4 mmol) of the ester from Step A in 25 ml of ether was added

dropwise to a stirred suspension of 0.38 g (10 mmol) of lithium aluminum hydride in 75 ml of ether at 0°C under nitrogen. After completion of the addition, the mixture was stirred at room temperature for 15 minutes, refluxed for 1 hour, cooled in ice and treated with successive additions of 0.4 ml of water, 0.35 ml of 20% (w/v) aqueous sodium hydroxide and 1.1 ml of water. The resulting mixture was stirred at 0°C for 0.5 hour, treated with anhydrous MgSO_4 , stirred for 15 minutes and filtered. The filtrate was concentrated in vacuo to give 3.08 g (11.3 mmol) (99%) of pale yellow oily product which was used directly in the next step without purification.

nmr (CDCl_3) δ : 1.45-1.7 (2H, m), 2.25 (6H, s), 2.33 (3H, s), 2.45-2.7 (2H, m), 3.45 (2H, t, $J=6\text{Hz}$), 6.85 (H, bs), 6.95-7.2 (4H, m).

Step C: Preparation of 2-(3-Bromopropyl)-4'-fluoro-3,3',5-trimethyl-1,1'-biphenyl

A solution of 1.08 g (4 mmol) of PBr_3 in 10 ml of ether was added dropwise to a stirred solution of 3.08 g (11.3 mmol) of the alcohol from Step B in 40 ml of ether at 0°C. The mixture was stirred at room temperature for 1 hour, refluxed for 0.5 hour, cooled to room temperature, poured into ice water and extracted with ether. The extract was washed with water and saturated aqueous sodium bicarbonate, dried over MgSO_4 , filtered and evaporated to dryness in vacuo. The residue was purified by flash chromatography on silica gel (230-400 mesh) by elution with methylene chloride/hexane (1:3, v/v). Combination and evaporation of the appropriate fractions gave the

desired bromide as a pale yellow oil, (1.9 g, 5.67 mmol, 48% overall Steps A, B and C).

nmr (CDCl_3) δ : 1.7-2.0 (2H, m), 2.27 (6H, a methyl singlet and a methyl doublet), 2.35 (3H, s), 2.55-2.8 (2H, m), 3.23 (2H, t, $J=6\text{Hz}$), 6.85 (H, bs), 6.95-7.2 (4H, m).

Step D: Preparation of 4'-Fluoro-3,3',5-trimethyl-2-(3-nitropropyl)-1,1'-biphenyl

10 A solution of 1.90 g (5.66 mmol) of the bromopropyl compound from Step C in 5 ml of ether was added to a stirred suspension of 1.31 g (8.5 mmol) of silver nitrite in 5 ml of ether at 0°C . The resulting mixture was stirred under nitrogen at 0°C 15 for 7 hours, warmed to room temperature and stirred for an additional 16 hours. Another 1.0 g of silver nitrite was added and stirring was continued for another 20 hours.

The reaction mixture was filtered and the 20 filtrate was concentrated to leave a residue which was purified by flash chromatography on silica gel (230-400 mesh) by elution with methylene chloride/hexane (1:4, v/v) to give, first, the recovered starting bromide, then the desired product, (0.64 g, 25 2.12 mmol, 78%). nmr (CDCl_3) δ : 1.8-2.2 (2H, m), 2.30 (6H, a methyl singlet and a methyl doublet), 2.33 (3H, s), 2.5-2.7 (2H, m), 4.18 (2H, t, $J=6\text{Hz}$), 6.88 (H, bs), 7.0-7.2 (4H, m). IR (neat) 1550, 1500 cm^{-1} .

30

Step E: Preparation of Methyl 3-[2-(4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl)ethyl]-4,5-dihydro-5-isoxazoleacetate

A solution of 0.1 g (1.0 mmol) of methyl
5 3-butenate and 0.174 ml (1.6 mmol) of phenyl
isocyanate in 1 ml of toluene was added with stirring
to a solution of 0.240 g (0.8 mmol) of the nitro-
propyl compound from Step D and 2 drops of triethyl-
amine in 1 ml of toluene. The resulting mixture was
10 stirred at room temperature for 3 hours. Additional
quantities of methyl 3-butenate (0.1 ml), triethyl-
amine (0.1 ml) and phenyl isocyanate (0.15 ml) were
added successively and stirring was continued over-
night (18 hours). The mixture was filtered and the
15 filtrate was concentrated in vacuo to a residue which
was purified by flash chromatography on silica gel
(230-400 mesh), first being eluted with methylene
chloride to remove the impurities. Continued elution
with acetone/methylene chloride (1:50, v/v) gave the
20 desired product (0.218 g, 0.57 mmol, 71%) as a pale
viscous oil. nmr (CDCl_3) δ : 2.28 (6H, s), 2.32 (3H,
s), 2.2-3.0 (6H, m), 3.70 (3H, s), 4.6-5.0 (H, m),
6.85 (H, bs), 7.0-7.2 (4H, m). IR (neat) 1735 cm^{-1} .
Analysis calculated for $\text{C}_{23}\text{H}_{26}\text{FNO}_3$: C 72.04;
25 H, 6.83; N, 3.65.
Found: C, 72.35; H, 6.99; N, 3.88.

Step F: Preparation of Methyl 7-(4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl)-3-hydroxy-5-oxoheptanoate

30 A mixture of 0.1 g (0.26 mmol) of the
isoxazoline from Step E, 50 mg of 10% palladium on
carbon catalyst and 48 mg (0.78 mmol) of boric acid

in 3 ml of methanol and 0.3 ml of water was stirred under hydrogen (1 atmosphere) at room temperature for 2.5 hours. The mixture was filtered and the filtrate was poured into brine and extracted with ether. The
 5 ethereal extract was washed with 5% (w/v) aqueous sodium bicarbonate solution, dried (MgSO_4), filtered and evaporated to dryness to give 92 mg (0.23 mmol, 89%) as a pale yellow oil. nmr (CDCl_3)
 8: 2.30 (6H, a methyl singlet and a methyl doublet),
 10 2.33 (3H, s), 2.35-2.5 (6H, m), 2.75-2.85 (2H, m), 3.30 (H, d), 3.70 (3H, s), 4.37 (H, m), 6.83 (H, bs), 6.95-7.1 (4H, m). IR (neat) 3450, 1710 cm^{-1} .

Step G: Preparation of 7-(4'-fluoro-3,3',5-trimethyl-
 15 [1,1'-biphenyl]-2-yl)-3-hydroxy-5-oxoheptanoic acid

Employing the procedure substantially as described in Example 1, Step E, the ester from Step G of this Example 2 is saponified to the subject 5-keto
 20 acid.

Employing the procedure substantially as described in Example 2, Steps A through G, but substituting for the chloromethylbiphenyl employed in
 Step A thereof, equimolar amounts of the chloromethyl
 25 compounds described in Table II, there are produced the 5-keto esters, salts and acids also described in Table II in accordance with the following reaction sequence:

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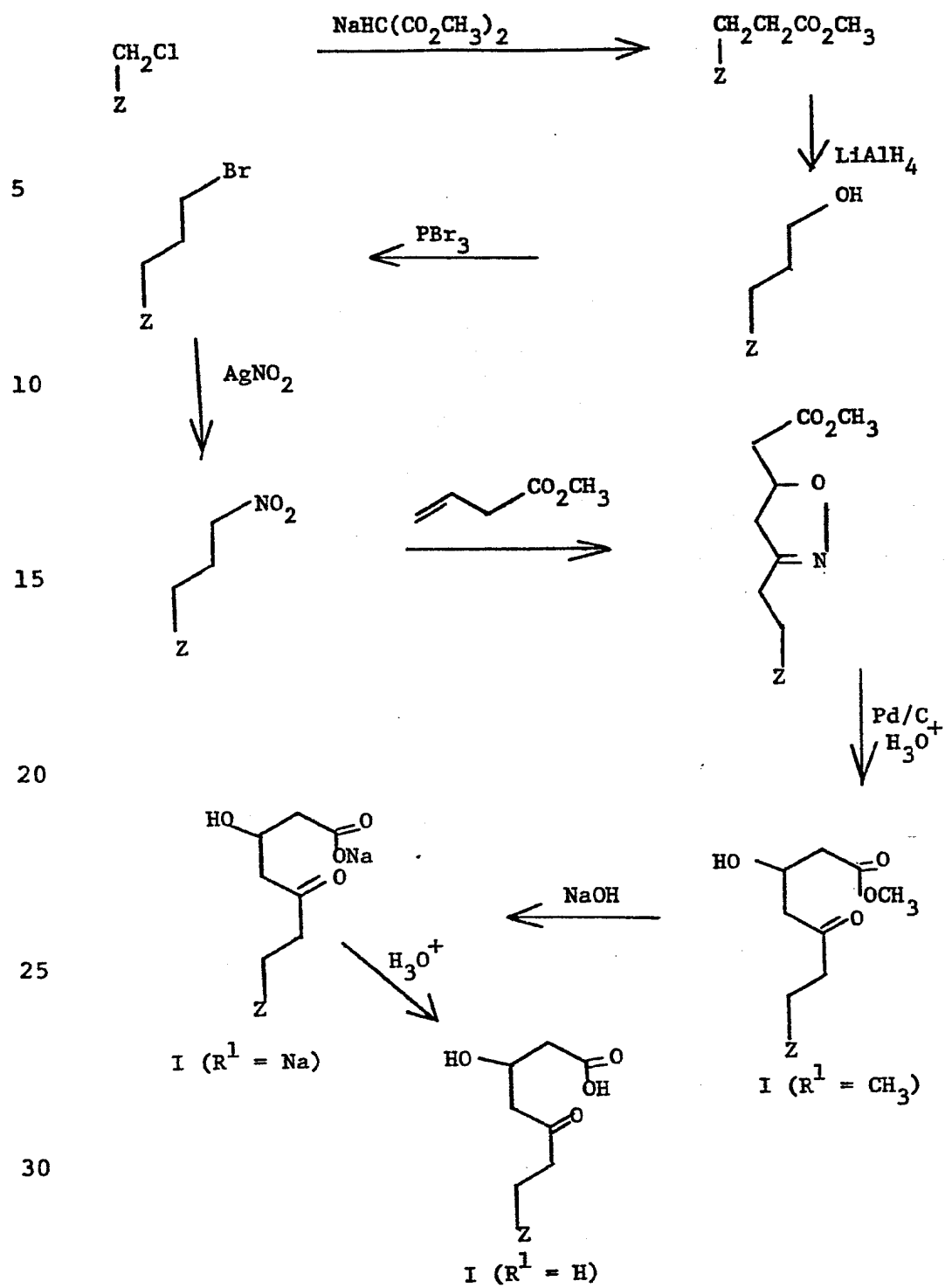
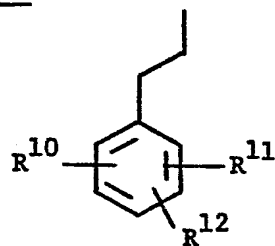


TABLE II

5

$$\begin{array}{c} | \\ \text{E} \\ | \\ \text{Z} \end{array}$$

=



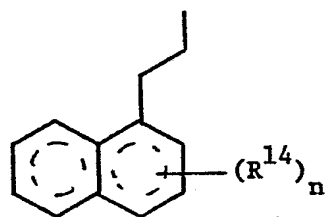
10

	R^{10}	R^{11}	R^{12}
	6-(4-fluorophenyl) -	2-chloro	4-chloro
	6-(4-chlorophenyl) -	2-chloro	4-chloro
15	6-(3,4-dichlorophenyl) -	2-chloro	4-chloro
	6-(4-fluoro-3-methylphenyl) -	2-chloro	4-chloro
	6-(3,4-dichlorophenyl) -	2-methyl	4-methyl
	6-(3,4-dimethylphenyl) -	2-chloro	4-chloro
	6-(3,4-dichlorophenyl) -	2-methyl	5-methyl
20	6-(4-fluorophenyl) -	2-methyl	4-methyl
	6-(4-fluoro-3-methylphenyl) -	2-methyl	4-chloro
	6-(4-fluorobenzyloxy)	2-chloro	4-chloro
	6-(4-fluoro-3-methylphenyl) -	2-chloro	4-methyl

25

$$\begin{array}{c} | \\ \text{E} \\ | \\ \text{Z} \end{array}$$

=



30

	<u>n</u>	<u>R¹⁴</u>	
	1	2-methyl	naphthyl
	0	-	naphthyl
5	2	2,6-dimethyl	naphthyl
	1	2-methyl	5,6,7,8-tetra- hydronaphthyl

EXAMPLE 3

10 7-(2,4-Dichlorophenyl)-3-hydroxy-5-oxoheptanoic acid
Step A: Preparation of Methyl 7-(2,4-Dichlorophenyl)-
3-hydroxy-5-oxo-6-heptenoate

Activated manganese dioxide (40 g) was added
to a solution of methyl 7-(2,4-dichlorophenyl)-3,5-
15 dihydroxy-6-heptenoate (6.8 g, 21.3 mmol) in
chloroform (600 mL) and the black suspension was
vigorously stirred at ambient temperature for 20
hours. After filtration and evaporation of the
solvent the residual amber oil (4.5 g, 1 major spot
20 on TLC with R_f 0.61 on Whatman MK6F silica using
CHCl₃-MeOH; 19:1 as eluent) was chromatographed on
a Still column to obtain the product (3.9 g, 58%) as
a pale yellow oil which solidified on standing, m.p.
77-79°C; NMR (CDCl₃) δ : 2.57 (2H, d, J=6Hz,
25 -CH₂CO₂-), 2.93 (2H, d, J=6Hz, -CH₂-CO-), 3.70
(3H, s, -CO₂CH₃), 4.4-4.8 (H, m, -CH(OH)-), 6.67
(H, d, J=16 Hz, =CH-CO), 7.1-7.7 (3H, m. ArH), 7.93
(H, d, J=16 Hz, =CH).

Analysis for C₁₄H₁₄Cl₂O₄.

30 Calcd.: C, 53.02; H, 4.45.

Found: C, 53.25; H, 4.50.

Step B: Preparation of Methyl 7-(2,4-Dichlorophenyl)-3-hydroxy-5-oxoheptanoate

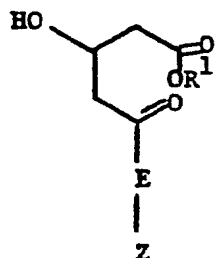
Tributyltin hydride (450 μ L, 1.7 mmol) was added dropwise over 1-1/2 hours to a stirred solution of the ene-one ester from Step A (320 mg, 1 mmol) and tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.03 mmol) in dry THF (5 mL) at ambient temperature under N_2 . After standing at 20°C overnight the light-brown solution was distributed between water (100 mL) and ether (150 mL). The organic layer was separated and washed with water (2 x 100 mL), dried and evaporated. The residual oil (1 major spot on TLC with R_f 0.39 vis-a-vis 0.35 for the starting ene-one ester on Whatman MK6F silica using $CHCl_3$ -MeOH; 99:1 as eluent) was chromatographed on a Still column to obtain the product (260 mg, 81%) as a pale amber gum; NMR ($CDCl_3$) δ : 2.5-2.525 (2H, m, $-CH_2CO_2-$), 2.57-2.73 (2H, m, $-COCH_2C(OH)-$), 2.77 (2H, t, $J=7.5$ Hz, $Ar-CH_2CH_2CO-$), 2.98 (2H, t, $J=7.5$ Hz, $Ar-CH_2CH_2CO-$), 3.71 (3H, s, $-CO_2CH_3$), 4.45-4.51 (H, m, $-CH(OH)-$).
Analysis for $C_{14}H_{16}Cl_2O_4$
Calcd.: C, 52.68, H, 5.05.
Found: C, 52.47; H, 5.20.

Step C: Preparation of 7-(2,4-dichlorophenyl)-3-hydroxy-5-oxoheptanoic acid

Employing the procedure substantially as described in Example 1, Step E, the ester from Step B of this Example 3 is saponified to the subject 5-oxo acid.

WHAT IS CLAIMED IS

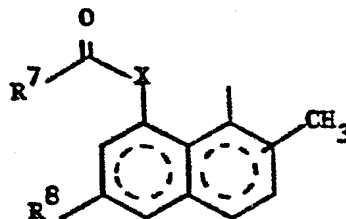
1. A compound of structural formula:



wherein:

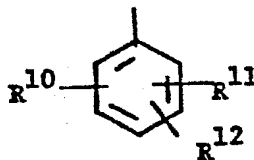
- 20 R^1 is 1) hydrogen,
 2) C_{1-4} alkyl,
 3) 2,3-dihydroxypropyl,
 4) alkali metal cation, or
- 25 5) ammonium of formula $NR^3R^4R^5R^6$
 wherein R^3 , R^4 , R^5 and R^6 are
 independently hydrogen or C_{1-4} alkyl or
 two of R^3 , R^4 , R^5 and R^6 are
 joined together to form a 5- or
 6-membered heterocycle with the nitrogen
 to which they are attached;
- 30 E is $-CH_2CH_2-$, $-CH=CH-$, or $-(CH_2)_3-$; and

z. is 1)



wherein X is -O- or -NR⁹ wherein R⁹ is hydrogen or C₁₋₃alkyl;
R⁷ is C₂₋₈alkyl; and
R⁸ is hydrogen or -CH₃;

2)

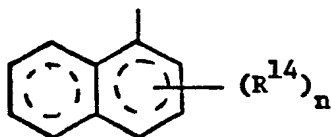


wherein R¹⁰, R¹¹ and R¹² are independently

- a) hydrogen,
- b) halogen, such as bromo, chloro or fluoro,
- c) C₁₋₄alkyl,
- d) halo-C₁₋₄alkyl,
- e) phenyl either unsubstituted or substituted with one or more of
 - i) C₁₋₄alkoxy,
 - ii) C₁₋₄alkyl,
 - iii) C₂₋₈alkanoyloxy,
 - iv) halo-C₁₋₄alkyl, or
 - v) halo,
- f) OR¹³ wherein R¹³ is
 - i) hydrogen,
 - ii) C₂₋₈alkanoyl,
 - iii) benzoyl,

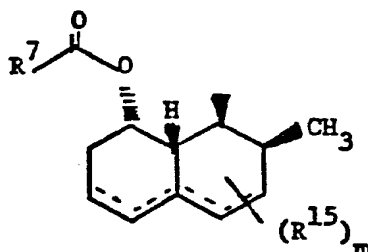
- iv) phenyl,
 v) halophenyl,
 vi) phenyl- C_{1-3} alkyl, either
 5 unsubstituted or substituted with
 one or more of halogen,
 C_{1-4} alkoxy, C_{1-4} alkyl or
 halo- C_{1-4} alkyl,
 vii) C_{1-9} alkyl,
 viii) cinnamyl,
 10 ix) halo- C_{1-4} alkyl,
 x) allyl,
 xi) C_{3-6} cycloalkyl- C_{1-3} alkyl, or
 xii) adamantyl- C_{1-3} alkyl;

3)



wherein n is 0-2 and R^{14} is halo or
 C_{1-4} alkyl; and

4)



wherein the dotted lines represent
 30 possible double bonds there being 0, 1 or
 2 double bonds;

m represents 1, 2 or 3; and

- R^{15} is
- 1) methyl,
 - 2) hydroxy,
 - 3) C_{1-4} alkoxy,
 - 4) oxo, or
 - 5) halo.

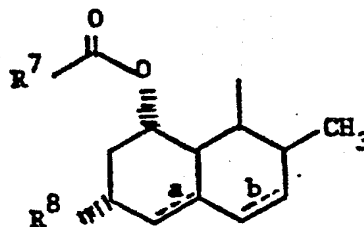
5

2. The compound of Claim 1 wherein:
 R^1 is hydrogen, an alkali metal cation or an ammonium cation;

10 E is $-CH=CH-$ or $-CH_2CH_2-$; and

Z is 1)

15

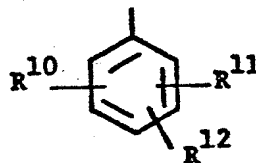


20

wherein $R^{7H}C=O$ is 2(S)-methylbutyryl or 2,2-dimethylbutyryl;

25

2)



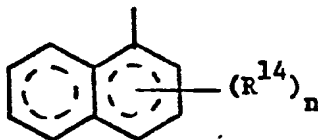
30

wherein R^{10} , R^{11} and R^{12} are independently

- a) halogen,
- b) C_{1-4} alkyl,
- c) halo- C_{1-4} alkyl,

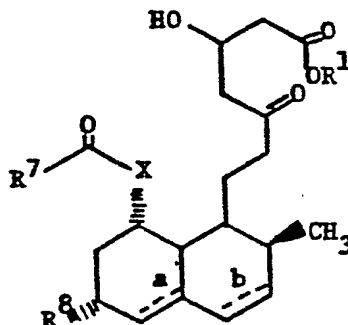
- d) phenyl with 1 to 3 substituents selected from halo, C_{1-4} alkyl or C_{1-4} alkoxy,
- e) OR^{13} , wherein R^{13} is
- i) phenyl,
 - ii) halophenyl, or
 - iii) phenyl substituted with 1-3 substituents selected from halogen and C_{1-4} alkyl,
 - iv) phenyl- C_{1-3} alkyl, either unsubstituted or substituted with one or more of halogen, C_{1-4} alkoxy, C_{1-4} alkyl or halo- C_{1-4} alkyl; or

3)



wherein n is 0, 1 or 2, and R^{14} is methyl, and the ring system is naphthyl, or 5,6,7,8-tetrahydronaphthyl.

3. The compound of Claim 2 selected from:

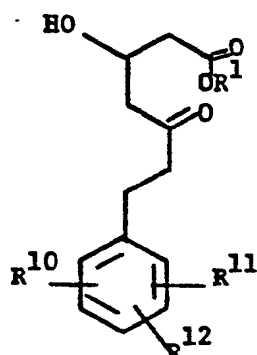


	$\text{R}^7 \overset{\text{O}}{\parallel} \text{C}-$	R^8	X	a*	b
5	2(S)-methylbutyryl	$-\text{CH}_3$	O	single	double
	2(S)-methylbutyryl	$-\text{CH}_3$	O	single	single
	2(R)-methylbutyryl	$-\text{CH}_3$	O	double	double
	2,2-dimethylbutyryl	$-\text{CH}_3$	O	double	double
	2,2-dimethylbutyryl	$-\text{CH}_3$	O	single	double
	2,2-dimethylbutyryl	$-\text{CH}_3$	O	single	single
10	acetyl	$-\text{CH}_3$	O	double	double
	2(S)-methylbutyryl	H	O	double	double
	2(S)-methylbutyryl	H	O	single	single
	2,2-dimethylbutyryl	H	O	double	double
	2,2-dimethylbutyryl	H	O	single	single
	2,2-dimethylbutyryl	$-\text{CH}_3$	NH	single	single
15	2-methyl-2-ethyl- butyryl	$-\text{CH}_3$	NH	single	single
	2-methylbutyryl	$-\text{CH}_3$	NH	single	single
	4-fluorobenzoyl	$-\text{CH}_3$	NH	single	single
	4-fluorophenyl-	$-\text{CH}_3$	NH	single	single
	acetyl				
	4- <u>tert</u> -butylbenzoyl	$-\text{CH}_3$	NH	single	single
20	acetyl	$-\text{CH}_3$	NH	double	double
	acetyl	$-\text{CH}_3$	NCH ₃	single	single
	2,2-dimethylbutyryl	$-\text{CH}_3$	NCH ₃	single	single
	2,2-dimethylbutyryl	$-\text{CH}_3$	NH	double	double
	2,2-dimethylbutyryl	$-\text{CH}_3$	NH	double	double
	2,2-dimethylbutyryl	$-\text{CH}_3$	NH	double	double

* When a=single bond, the rings are trans-fused.

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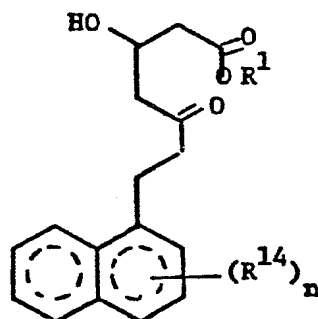
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R^{10}	R^{11}	R^{12}
6-(4-fluoro-3-methylphenyl)-	2-methyl	4-methyl
6-(4-fluorophenyl)-	2-chloro	4-chloro
6-(4-chlorophenyl)-	2-chloro	4-chloro
6-(3,4-dichlorophenyl)	2-chloro	4-chloro
6-(4-fluoro-3-methylphenyl)	2-chloro	4-chloro
6-(3,4-dichlorophenyl)	2-methyl	4-methyl
6-(3,5-dimethylphenyl)-	2-chloro	4-chloro
6-(3,4-dichlorophenyl)-	2-methyl	5-methyl
6-(4-fluorophenyl)	2-methyl	4-methyl
6-(4-fluoro-3-methylphenyl)-	2-methyl	4-chloro
6-(4-fluorobenzoyloxy)	2-chloro	4-chloro
6-(4-fluoro-3-methylphenyl)-	2-chloro	4-methyl

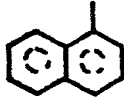
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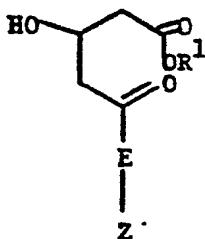
5	<u>n</u>	<u>R¹⁴</u>	
	1	2-methyl	naphthyl
	0	-	naphthyl
	2	2,6-dimethyl	naphthyl
	1	2-methyl	5,6,7,8-tetra- hydronaphthyl

4. An antihypercholesterolemic pharmaceutical composition comprising a pharmaceutical carrier and an effective antihypercholesterolemic amount of a compound as claimed in Claim 1.

5. The formulation of Claim 4 wherein the antihypercholesterolemic compound is as claimed in Claim 2.

6. The formulation of Claim 5 wherein the antihypercholesterolemic compound is as claimed in Claim 3.

7. A process for the preparation of a compound of structural formula:



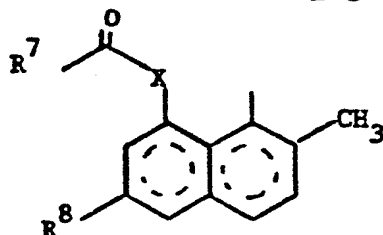
wherein:

R^1 is 1) hydrogen,
2) C_{1-4} alkyl,
3) 2,3-dihydroxypropyl,
4) alkali metal cation, or

5) ammonium of formula $NR^3R^4R^5R^6$
wherein R^3 , R^4 , R^5 and R^6 are
independently hydrogen or C_{1-4} alkyl or
two of R^3 , R^4 , R^5 and R^6 are
joined together to form a 5- or
6-membered heterocycle with the nitrogen
to which they are attached;

E is $-CH_2CH_2-$, $-CH=CH-$, or $-(CH_2)_3-$; and

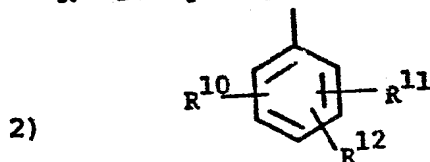
Z is 1)



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wherein X is -O- or $>NR^9$ wherein R^9 is hydrogen or C_{1-3} alkyl;
 R^7 is C_{2-8} alkyl; and
 R^8 is hydrogen or $-CH_3$;

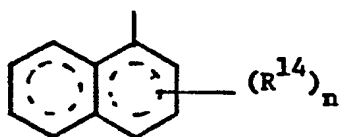


wherein R^{10} , R^{11} and R^{12} are independently

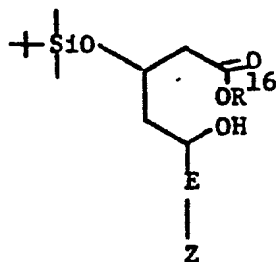
- a) hydrogen,
- b) halogen, such as bromo, chloro or fluoro,
- c) C_{1-4} alkyl,
- d) halo- C_{1-4} alkyl,
- e) phenyl either unsubstituted or substituted with one or more of
 - i) C_{1-4} alkoxy,
 - ii) C_{1-4} alkyl,
 - iii) C_{2-8} alkanoyloxy, or
 - iv) halo- C_{1-4} alkyl,
 - v) halo,
- f) OR^{13} wherein R^{13} is
 - i) hydrogen,
 - ii) C_{2-8} alkanoyl,
 - iii) benzoyl,
 - iv) phenyl,
 - v) halophenyl,
 - vi) phenyl- C_{1-3} alkyl, either unsubstituted or substituted with one or more of halogen,

- C_{1-4} alkoxy, C_{1-4} alkyl or
 halo- C_{1-4} alkyl,
 vii) C_{1-9} alkyl,
 viii) cinnamyl,
 5 ix) halo- C_{1-4} alkyl,
 x) allyl,
 xi) C_{3-6} cycloalkyl- C_{1-3} alkyl, or
 xii) adamantyl- C_{1-3} alkyl;

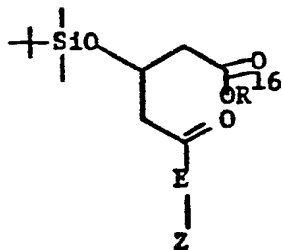
3)



wherein n is 0-2 and R^{14} is halo or
 C_{1-4} alkyl, which comprises treating a
 compound of structural formula:



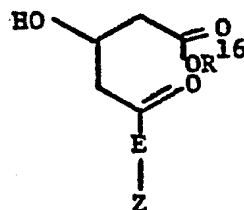
wherein R^{16} is C_{1-4} alkyl, with an
 oxidizing agent to produce the compound
 of structural formula:



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followed by desilylation to produce the compound of structural formula:



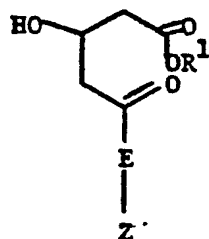
10

followed by treatment with alkali to produce the product wherein R¹⁶ is an alkali metal cation, followed by acidification to produce the compound wherein R¹⁶ is a hydrogen ion.

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CLAIMS FOR THE CONTRACTING STATE ATWHAT IS CLAIMED IS:

1. A process for the preparation of a compound of structural formula:



wherein:

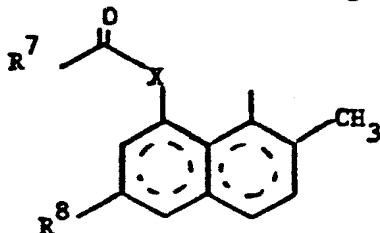
R¹ is

- 1) hydrogen,
- 2) C₁₋₄alkyl,
- 3) 2,3-dihydroxypropyl,
- 4) alkali metal cation, or

- 5) ammonium of formula $\text{NR}^3\text{R}^4\text{R}^5\text{R}^6$ ⁺ wherein R³, R⁴, R⁵ and R⁶ are independently hydrogen or C₁₋₄alkyl or two of R³, R⁴, R⁵ and R⁶ are joined together to form a 5- or 6-membered heterocycle with the nitrogen to which they are attached;

E is -CH₂CH₂-, -CH=CH-, or -(CH₂)₃-; and

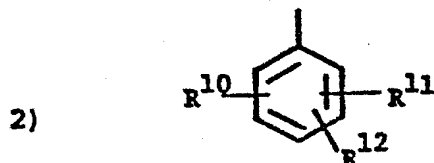
Z is 1)



- 2 -

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wherein X is -O- or NR^9 wherein R^9
 is hydrogen or C_{1-3} alkyl;
 R^7 is C_{2-8} alkyl; and
 R^8 is hydrogen or $-\text{CH}_3$;



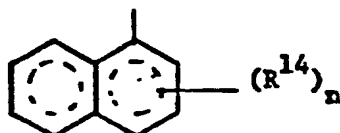
wherein R^{10} , R^{11} and R^{12} are
 independently

- a) hydrogen,
- b) halogen, such as bromo, chloro or fluoro,
- c) C_{1-4} alkyl,
- d) halo- C_{1-4} alkyl,
- e) phenyl either unsubstituted or substituted with one or more of
 - i) C_{1-4} alkoxy,
 - ii) C_{1-4} alkyl,
 - iii) C_{2-8} alkanoyloxy, or
 - iv) halo- C_{1-4} alkyl,
 - v) halo,
- f) OR^{13} wherein R^{13} is
 - i) hydrogen,
 - ii) C_{2-8} alkanoyl,
 - iii) benzoyl,
 - iv) phenyl,
 - v) halophenyl,
 - vi) phenyl- C_{1-3} alkyl, either unsubstituted or substituted with one or more of halogen,

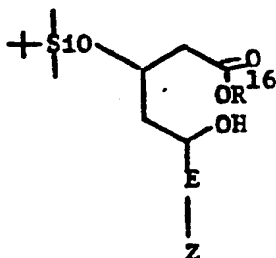
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- C_{1-4} alkoxy, C_{1-4} alkyl or
 halo- C_{1-4} alkyl,
 vii) C_{1-9} alkyl,
 viii) cinnamyl,
 5 ix) halo- C_{1-4} alkyl,
 x) allyl,
 xi) C_{3-6} cycloalkyl- C_{1-3} alkyl, or
 xii) adamantyl- C_{1-3} alkyl;

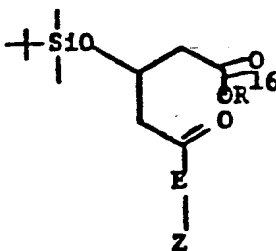
3)



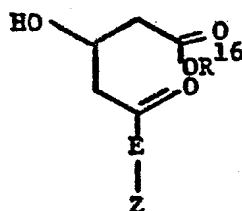
15 wherein n is 0-2 and R^{14} is halo or
 C_{1-4} alkyl, which comprises treating a
 compound of structural formula:



25 wherein R^{16} is C_{1-4} alkyl, with an
 oxidizing agent to produce the compound
 of structural formula:



followed by desilylation to produce the compound of structural formula:



10 followed by treatment with alkali to produce the product wherein R^{16} is an alkali metal cation, followed by acidification to produce the compound wherein R^{16} is a hydrogen ion.

15

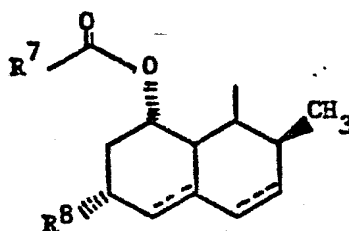
2. The process of Claim 1 wherein:

R^1 is hydrogen, an alkali metal cation or an ammonium cation;

E is $-CH=CH-$ or $-CH_2CH_2-$; and

20

Z is 1)

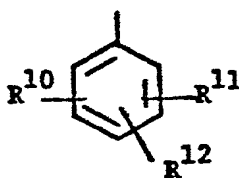


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wherein R^7C- is 2(S)-methylbutyryl or 2,2-dimethylbutyryl;

30

2)



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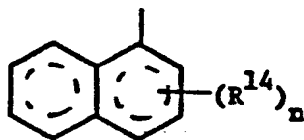
wherein R^{10} , R^{11} and R^{12} are independently

- a) halogen,
- b) C_{1-4} alkyl,
- c) halo- C_{1-4} alkyl,
- d) phenyl with 1 to 3 substituents selected from halo, C_{1-4} alkyl or C_{1-4} alkoxy,

e) OR^{13} , wherein R^{13} is

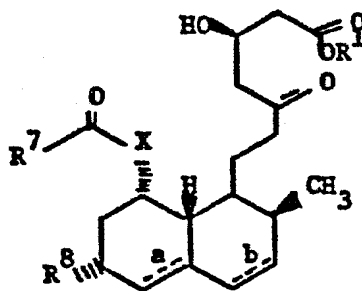
- i) phenyl,
- ii) halophenyl, or
- iii) phenyl substituted with 1-3 substituents selected from halogen and C_{1-4} alkyl; or
- iv) phenyl- C_{1-3} alkyl, either unsubstituted or substituted with one or more of halogen, C_{1-4} alkoxy, C_{1-4} alkyl, or halo- C_{1-4} alkyl; or

3)



wherein n is 0, 1 or 2, and R^{14} is methyl and the ring system is naphthalene or 5,6,7,8-tetrahydronaphthalene.

3. The process of Claim 2 for the preparation of a compound selected from:

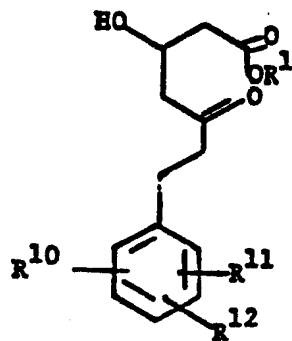


	$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}^7\text{C}- \end{array}$	R^8	X	a*	b
5	2(S)-methylbutyryl	$-\text{CH}_3$	O	single	double
	2(S)-methylbutyryl	$-\text{CH}_3$	O	single	single
	2(R)-methylbutyryl	$-\text{CH}_3$	O	double	double
	2,2-dimethylbutyryl	$-\text{CH}_3$	O	double	double
10	2,2-dimethylbutyryl	$-\text{CH}_3$	O	single	double
	2,2-dimethylbutyryl	$-\text{CH}_3$	O	single	single
	acetyl	$-\text{CH}_3$	O	double	double
	2(S)-methylbutyryl	H	O	double	double
	2(S)-methylbutyryl	H	O	single	single
15	2,2-dimethylbutyryl	H	O	double	double
	2,2-dimethylbutyryl	H	O	single	single
	2,2-dimethylbutyryl	$-\text{CH}_3$	NH	single	single
20	2-methyl-2-ethyl-butyl	$-\text{CH}_3$	NH	single	single
	2-methylbutyryl	$-\text{CH}_3$	NH	single	single
	4-fluorobenzoyl	$-\text{CH}_3$	NH	single	single
	4-fluorophenyl-acetyl	$-\text{CH}_3$	NH	single	single
25	4-tert-butylbenzoyl	$-\text{CH}_3$	NH	single	single
	acetyl	$-\text{CH}_3$	NH	double	double
	acetyl	$-\text{CH}_3$	NCH ₃	single	single
30	2,2-dimethylbutyryl	$-\text{CH}_3$	NCH ₃	single	single
	2,2-dimethylbutyryl	$-\text{CH}_3$	NH	double	double

* When a=single bond, the rings are trans-fused.

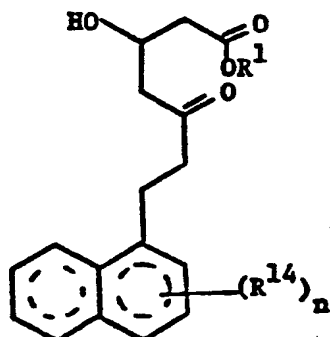
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	R ¹⁰	R ¹¹	R ¹²
10	6-(4-fluoro-3-methylphenyl)-	2-methyl	4-methyl
	6-(4-fluorophenyl)-	2-chloro	4-chloro
	6-(4-chlorophenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)	2-chloro	4-chloro
15	6-(4-fluoro-3-methylphenyl)	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)	2-methyl	4-methyl
	6-(3,5-dimethylphenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)-	2-methyl	5-methyl
	6-(4-fluorophenyl)	2-methyl	4-methyl
20	6-(4-fluoro-3-methylphenyl)-	2-methyl	4-chloro
	6-(4-fluorobenzoyloxy)	2-chloro	4-chloro
	6-(4-fluoro-3-methylphenyl)	2-chloro	4-methyl

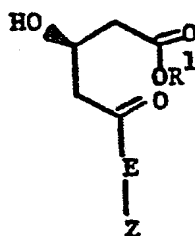
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5	<u>n</u>	<u>R¹⁴</u>	
	1	2-methyl	naphthyl
	0	-	naphthyl
	2	2,6-dimethyl	naphthyl
	1	2-methyl	5,6,7,8-tetrahydronaphthyl

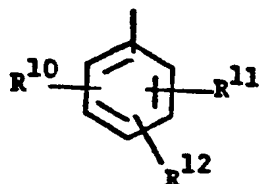
- 10 4. A process for the preparation of a compound of formula



- 15
- wherein
- 20 R¹ is
- 1) hydrogen,
 - 2) C₁₋₄alkyl,
 - 3) 2,3-dihydroxypropyl,
 - 4) alkali metal cation, or
 - 25 5) ammonium of formula $\text{NR}^3\text{R}^4\text{R}^5\text{R}^6$ wherein R³, R⁴, R⁵ and R⁶ are independently hydrogen or C₁₋₄alkyl or two of R³, R⁴, R⁵ and R⁶ are jointed together to form a 5- or
 - 30 6-membered heterocycle with the nitrogen to which they are attached;
- E is -CH₂CH₂-, or -(CH₂)₃-; and

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Z. is 1)

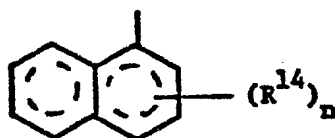


wherein R^{10} , R^{11} and R^{12} are independently

- a) hydrogen,
- b) halogen, such as bromo, chloro or fluoro,
- c) C_{1-4} alkyl,
- d) halo- C_{1-4} alkyl,
- e) phenyl either unsubstituted or substituted with one or more of
 - i) C_{1-4} alkoxy,
 - ii) C_{1-4} alkyl,
 - iii) C_{2-8} alkanoyloxy,
 - iv) halo- C_{1-4} alkyl, or
 - v) halo,
- f) OR^{13} wherein R^{13} is
 - i) hydrogen,
 - ii) C_{2-8} alkanoyl,
 - iii) benzoyl,
 - iv) phenyl,
 - v) halophenyl,
 - vi) phenyl- C_{1-3} alkyl, either unsubstituted or substituted with one or more of halogen, C_{1-4} alkoxy, C_{1-4} alkyl or halo- C_{1-4} alkyl,
 - vii) C_{1-9} alkyl,
 - viii) cinnamyl,

- ix) halo-C₁₋₄alkyl,
- x) allyl,
- xi) C₃₋₆cycloalkyl-C₁₋₃alkyl, or
- xii) adamantyl-C₁₋₃alkyl;

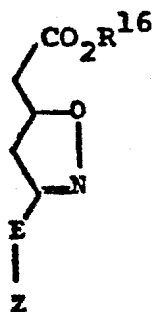
2)



wherein n is 0-2, and R^{14} is halo, or C₁₋₄ alkyl which comprises reacting the compounds



to produce the compound of structural formula:

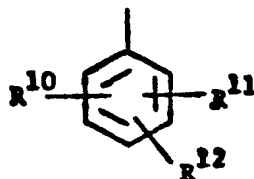


followed by catalytic reduction to produce the desired compound wherein R^1 is R^{16} ; followed by treatment with alkali to produce the product wherein R^1 is an alkali metal cation, followed by acidification to produce the compound wherein R^1 is a hydrogen ion.

5. The process of Claim 4 wherein:
 R^i is hydrogen, an alkali metal cation or an ammonium cation;

E is $-CH_2CH_2-$; and

Z is 1)



wherein R^{10} , R^{11} and R^{12} are independently

a) halogen,

b) C_{1-4} alkyl,

c) halo- C_{1-4} alkyl,

d) phenyl with 1 to 3 substituents selected from halo, C_{1-4} alkyl or C_{1-4} alkoxy,

e) OR^{13} , wherein R^{13} is

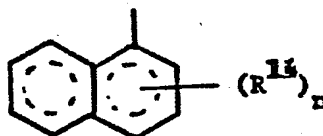
i) phenyl,

ii) halophenyl, or

iii) phenyl substituted with 1-3 substituents selected from halogen and C_{1-4} alkyl; or

iv) phenyl- C_{1-3} alkyl, either unsubstituted or substituted with one or more of halogen, C_{1-4} alkoxy, C_{1-4} alkyl, or halo- C_{1-4} alkyl; or

2)



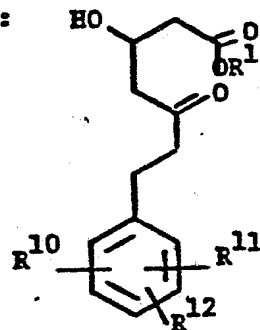
5

10

wherein n is 0, 1 or 2, and R^{14} is methyl and the ring system is naphthalene or 5,6,7,8-tetrahydronaphthalene.

6. The process of Claim 5 for preparation of a compound selected from:

15



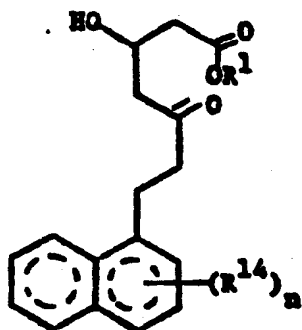
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R^{10}	R^{11}	R^{12}
6-(4-fluoro-3-methylphenyl)-	2-methyl	4-methyl
6-(4-fluorophenyl)-	2-chloro	4-chloro
6-(4-chlorophenyl)-	2-chloro	4-chloro
25 6-(3,4-dichlorophenyl)	2-chloro	4-chloro
6-(4-fluoro-3-methylphenyl)	2-chloro	4-chloro
6-(3,4-dichlorophenyl)	2-methyl	4-methyl
6-(3,5-dimethylphenyl)-	2-chloro	4-chloro
6-(3,4-dichlorophenyl)-	2-methyl	5-methyl
30 6-(4-fluorophenyl)	2-methyl	4-methyl
6-(4-fluoro-3-methylphenyl)-	2-methyl	4-chloro
6-(4-fluorobenzyloxy)	2-chloro	4-chloro
6-(4-fluoro-3-methylphenyl)-	2-chloro	4-methyl

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and



5

10

<u>n</u>
1
0
2
1

R¹⁴

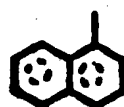
2-methyl

-

2,6-dimethyl

2-methyl

15



naphthyl

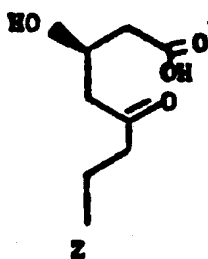
naphthyl

naphthyl

5,6,7,8-tetra-
hydronaphthyl

7. A process for the preparation of a compound of structural formula:

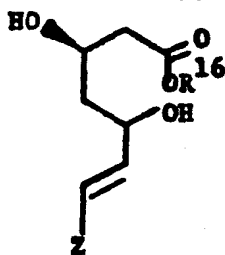
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25

wherein Z is as defined in Claim 1, which comprises treating a compound of structural formula:

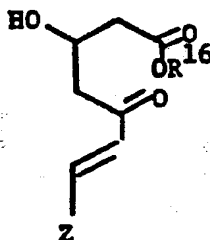
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with activated manganese dioxide to produce the compound of structural formula:



10 followed by treatment with tri-n-butyltin hydride and tetrakis (triphenylphosphine)palladium (0).